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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WOITACH, JOSEPH T	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/841,730	LEE ET AL.	
	Examiner	Art Unit	
	Joseph T. Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,13,14,20 and 40-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,13,14,20 and 40-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This application filed April 24, 2001, is a continuation in part of 09/626,896, filed July 7, 2000, which is a continuation in part of 09/485,046, filed May 5, 2000, which a national stage filing of PCT/US98/15598, filed July 28, 1998, which claims benefit to US provisional application 60/054,461, filed August 1, 1997.

Applicants' amendment filed October 27, 2003, has been received and entered. The specification has been amended. Claims 4, 6-12, 15-19 and 21-39 have been canceled. Claims 1, 2, 3, 5, 20, 40-42 have been amended. Claims 43-45 have been added.

Claims 1-3, 5, 13, 14, 20, 40-45 are pending.

Election/Restriction

Newly added claims 43-45 are drawn to the elected invention and therefore will be included in the instant examination. Applicant's election with traverse of Group I, in Paper No. 9 was acknowledged. Claims previously withdrawn to a non-elected invention have been canceled and no new arguments in traverse of the restriction requirement have been provided (see section B of Applicants' amendment).

Claims 1-3, 5, 13, 14, 20, 40-45 are pending and currently under examination as they are drawn to a transgenic non-human mammal comprising a transgene encoding a truncated Activin Type II receptor.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

Applicants point out specific support for the instantly claimed invention in both 09/626,896 and 09/485,046. See Applicants' amendment, Section C. Upon review of the portions indicated by Applicants in 09/626,896 and 09/485,046, Examiner agrees that the instant application is fully supported by 09/626,896 and 09/485,046. Therefore, the priority of the instant application is given afforded the filing date of July 28, 1998. With respect to provisional application 60/054,461, Applicants make no arguments. Upon review of 60/054,461 Examiner can not find similar support as provided in 09/626,896 and 09/485,046, therefore it is maintained that the instant application does not have priority to 60/054,461.

Specification

The objection to the disclosure because it contains an embedded hyperlink and/or other form of browser-executable code is withdrawn.

The amendments to the specification has obviated the basis of the objection. See Applicants' amendment Section D.

Claim Objections

Claims 1-3, 5, 13, 14, 20 and 40-42 objected to because the claims are broader than the elected invention reading on the non-elected inventions, and specifically in claim 1 because it appears to have a typographical error where it recites 'corresponding' twice in the final line of the claim is withdrawn.

Amendments to the claims has obviated the basis of both objections. See Applicants' amendment Section E.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, 13, 14, 20 and 40-42 stand and newly added claims 43-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a nucleic acid sequence which encodes a truncated Activin receptor IIB, wherein said truncated Activin receptor is a murine truncated receptor consisting of amino acid residues 1-174, operatively linked to the myosin light chain promoter

and 1/3 enhancer, wherein elevated expression levels of the Activin Type II B receptor result in an increased muscle mass as compared to a corresponding nontransgenic animal and methods of making said transgenic mouse, does not reasonably provide enablement for making or providing all transgenic non human animals nor other truncated Activin Type II receptors whose expression levels are regulated by other promoters encompassed by the claims.

Applicants summarize the basis of the rejection and note the amendment to the claims to encompass the production and use of non-human transgenic mammals (bridging pages 10-11). Applicants argue that methods of making transgenic are known in the art and that the instant specification references such methods as taught in issued as patents 6,140,522 and 6,218,596 (bottom of page 11). Summarizing the teaching of each of the cited references, Applicants argue that each of the references demonstrate in fact that transgenic mammals can be made, and that by providing the correct transgene expression a predictable phenotype can be obtained (pages 12-15). Furthermore, with respect to providing the proper promoters Applicants argue that the instant claims do not require a specific amount of increased muscle mass in transgenic non-human mammals and that in view of the art as a whole would have predicted that expression of any level of truncated Activin RII would be inversely correlated to increased muscle mass (page 16). Pointing to the general teaching in the instant specification and supporting evidence provided in newly provided references in Exhibits D and E, Applicants argue that it would have not required undue experimentation to make and use the instantly claimed invention (page 17).

See Applicants' amendment, Section F, pages 10-17. Applicants' arguments have been fully considered but not found persuasive.

The amendments to the claims are noted, in particular that the claims encompass non-human mammals and that the Activin Type II receptor that is expressed lacks kinase activity (see claim 1 and 40 for example). As noted in the previous office action, it is acknowledged that the specification provides a working example for a single transgenic mouse comprising a single transgene construct of a truncated murine Activin receptor IIB, whose expression is regulated by the myosin light chain promoter and 1/3 enhancer. The specification demonstrates that this particular transgene construct when inserted into the genome of a mouse by conventional methods of transgenics results in elevated expression levels of the Activin Type II B receptor and an increased muscle mass in said transgenic mouse. Examiner would agree that the methods for inserting a transgene into the genome of a mammal to generate a transgenic mammal are routine to the skilled artisan, however the basis of the rejection is not that such physical methods could not be practiced. Rather, the basis of the rejection focuses on the unpredictability of transgene behavior once it is inserted into the genome. Presently, in the art of transgenics while certain predictions are made regarding the use of specific promoters to achieve various levels of expression and the phenotypic affect of a transgene expression on the resulting transgenic, the true characteristics of the resulting transgenic animal can only be determined empirically. Examiner would agree that if sufficient number of species were made with a specific construct, a predictable pattern may emerge wherein the artisan would predict that other species may

demonstrate a similar phenotype. However, in the instant case only one species, a transgenic mouse made to express one specific Activin RIIB fragment has been made. In light of the unpredictability of transgenics, a single example is insufficient to provide a broad expectation that the same construct would work the same in other species as evidenced by Wall, Ebert and Mullins. Mullins *et al.* reviewing the art clearly states that "a given construct may react very differently from one species to another" (see Summary section). This observation is based on only a single construct. The instant claims encompass an enormous number of possible constructs with different promoter and different truncated forms of Activin Type II A and B receptors. Again, with respect to the breadth outside the single working example of a truncated Activin receptor the instant invention is prophetic relying on the teachings of the art for generating the claimed transgenic animals and methods of making and using. Given the unpredictability of the art of transgenics, the specification fails to provide a nexus by providing the necessary guidance to overcome the art recognized obstacles of generating transgenic animals. McPherron *et al.* (PNAS, 1997) was cited to teach that 'Unlike in mice, a myostatin null mutation in cattle causes an reduction in sizes in internal organs and only a modest increase in muscle mass' (page 12460, bottom of first column). Besides demonstrating that a mouse model is not predictive of other species, it is provided to demonstrate that proteins with related characteristics do not necessarily provide a predictable phenotype in other species. As demonstrated even in the instant specification expression of related truncated gene family members can result in a phenotype that is embryonic lethality and thus failure to produce or use

such transgenic animal (see GDR-11 mouse model, pages 118-119). Thus, even if a sequence is related to other gene family members the consequence of expressing a disrupted sequence can have unexpected consequences resulting in the inability to even generate a viable animal. To this end the instant claims require that a dominant negative form of Activin Typ II receptor be expressed or that the endogenous Activin Type II receptor be disrupted. The specification provides only one example of a dominant negative form of Activin Type IIB receptor, a truncated fragment represented by amino acids 1-174. There is no other guidance in the specification to what other sequences would provide this same dominant activity or whether the observations for the type IIB receptor are representative of type IIA. As currently amended encompass using any truncated form of Activin Type II receptor, type IIA or type IIB, however the structure-function relationship of these proteins has not been characterized in detail sufficient enough to obtain or practice the invention as claimed. As noted in the previous office action, the role of the Activin receptor *in vivo* is still a subject of active research and defining its specific role has been complicated by a redundancy in the TGF-β super family. In other tissues such as the pancreas Yamaoka *et al.* (1998) teach that the Activin receptor may be dispensable for normal development of islet cells (page 300, top of first column). However, while a redundancy may make a particular member of a the TGF-β super family dispensable in some cases, this does not simply extend to all types of alterations in the TGF-β super family or particular phenotypes produced by said alterations. Again, Yamaoka *et al.* (1998) teach that two alterations of TGF-β which should result in a null phenotype, over-expression of a TGF-β dominant negative mutant

and a TGF-β knockout construct, result in different affects on acinar cells in the pancreas (page 300, middle of first column). Thus, in view of the art even the expression of two different mutant transgenes from the TGF-β superfamily which should result in the same affect result in different phenotypes *in vivo* when expressed as transgenes.

With respect to the promoter it is noted that Wall generally supports the observation by stating that "our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." (see page 61, last paragraph). The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct are all important factors in controlling the expression of the transgene. While the state of the art of transgenics is such that one of skill in the art would be able to produce transgenic animals comprising a transgene of interest, it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. The are teaches that the level of expression of Activin Receptor II is critical in generating a particular phenotype (see results of Mathew *et al.*) . Thus, the level and the specificity of expression of a transgene as well as the phenotype of a transgenic animal produced are greatly dependent on the specific transgene construct used. In the instant case, because the art teaches that the phenotypic affect of the Activin receptor II is dose dependent, the specification fails to describe any other promoter besides the myosin light chain promoter and 1/3 enhancer which will provide the necessary levels of expression which will result in increase muscle mass as required by the claims.

As noted in the specification (page 132, paragraph 358) and in the art of record while a role for Activin in muscle development has been implicated because of the complexity of regulation of muscle development the specific mechanism and role of the Activin is not presently known. Given such species differences in the expression of various transgenes, in particular the TGF-β super family members, i.e. GDF-11, one of skill in the art would have been required to undergo undue experimentation to determine which promoters and specific transgene constructs would produce the desired phenotype in all non-human animals. In the instant case, the specific elements used in the construction of the DNA plasmids for use in generating the transgenic animals were not discovered by Applicant, rather they were derived from the art based on reports of their function in mice. Absent of evidence to the contrary, it is not clear that these elements would be functional in other animal species in the same manner as they have been demonstrated in mice. Further, given that other related members of the TGF-β super family result in different phenotypes in mice and cattle, there is no expectation that the phenotype observed for the transgenic mouse disclosed in the instant specification would extend to other non human mammals.

As discussed above, the claims are broad, encompassing any non-human transgenic animal containing the DNA constructs set forth in the claims. The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 *Ex parte Maizel*. Scope of Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). In view of the

quantity of experimentation necessary to determine the parameters listed above, the lack of direction or guidance provided by the specification, the absence of working examples for the demonstration or correlation to the production of transgenic animal models of any species, or other promoters which broadly meet the functional language encompassed by the claims, and the general unpredictable state of the art with respect to the generation of transgenic animals of all species, it would have required undue experimentation for one skilled in the art to make and/or use the claimed inventions as broadly claimed. Applicants' arguments are not found persuasive because the predictability purported by Applicants are not consistent with that demonstrated in the art of transgenics. It is noted that the arguments of counsel cannot take the place of evidence in the record (*In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716,718 (CCPA 1965)). In this case, the specification fails to provide the necessary guidance to overcome the art recognized limitations of generating transgenic animals with a predictable phenotype or that mouse models provide adequate evidence of a predictable phenotype in other species. Moreover, the breadth of the claims encompass embodiments such as the generation and use of any truncated form of Activin and the use of any promoter for expression. Given the reliance of the specification on the art to make the claimed invention and only one example of a mouse model it is maintained that due to the unpredictability of transgenics, the specification fails to provide sufficient evidence that the invention can be practiced in the full scope as claimed.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 41 and 42 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn.

Amendments to the claims has obviated the specific basis of the rejections. See Applicants amendment, final portion of Section F, starting on page 17.

Conclusion

No claim is allowed. As indicated in the previous office action, the claims are free of the art of record because the art fails to teach or make obvious a transgenic non human animal expressing a truncated Activin Type II receptor wherein said non human animal exhibits increased muscle mass. In particular, due to the unpredictability of transgene behavior and evidence that the activin receptor is involved in various organs and tissues (for example FSH regulation Crowley *et al.* US Patent 5,658,876) one would not have simply predicted that

expression of Activin Type II receptor mutants would result in increased muscle mass. The claims are free of the art of record, however the claims are subject to other rejections.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732. After January 12, 2004, the Examiner's telephone number will be (571) 272-0739.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. After January 12, 2004, Deborah Reynolds telephone number will be (571)272-0734.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141. After January 14, 2004, Dianiece Jacobs telephone number will be (571)272-0532.

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